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EXAMINER	
GRASER, JENNIFER E	

ART UNIT	PAPER NUMBER
1645	23

DATE MAILED: 11/07/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/142,970	Applicant(s) ACHTMAN ET AL.	
	Examiner Jennifer E. Graser	Art Unit 1645	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *02 September 2003* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *26-51* is/are pending in the application.

4a) Of the above claim(s) *42-50* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) *26-41 and 51* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office Action.

Acknowledgment and entry of the Amendment submitted 9/2/03, Paper No. 23D, is made. Claims 26-41 and 51 are currently pending.

Claim Rejections - 35 USC § 112

1. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

2. Claims 51 and 26-41 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 51 is vague and indefinite due to the parentheticals in lines 2 and 6 of the claim. It is unclear whether the T-independent antigen is required to be a polysaccharide or if it can be something else entirely. The parentheticals render the claim indefinite because it is unclear whether the limitation(s) enclosed within them are part of the claimed invention. . Additionally, it is unclear why there are parentheses around 'position 1'. Claim 51 states that the peptide "is able to elicit a T-cell dependent immune response to a T-independent antigen when conjugated to said antigen"; however, it is noted that solely the peptide is being claimed. Any peptide with the same structure will inherently perform this function.

Claim 51 is vague and indefinite because the claims do not contain the sequence identifier which places the recited domains in relation to the entire protein. The amino acid sequence for the IgA1 protease fragments being claimed should be referred to by sequence identifier. When a specific domain is identified by amino acid number, the sequence to which it refers must be included in the claims. While the specification can be used to provide definitive support, the claims are not read in a vacuum. Rather, the claim must be definite and complete in and of itself. Limitations from the specification will not be read into the claims. The claims as they stand are incomplete and fail to provide adequate structural properties to allow for one to identify what is being claimed.

Claim Rejections - 35 USC § 112-Enablement

3. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Claims 26-41 and 51 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for 'isolated peptides consisting of 40 to 200 amino acid residues, wherein the peptide comprises an amino acid sequence identical to SEQ ID NO: 1, 2, 3, 4 or 5' and for 'isolated peptides consisting of 40 to 200 amino acid residues, wherein the peptide comprises an amino acid sequence identical to SEQ ID NO: 1, 2, 3, 4 or 5 wherein the peptide begins with the amino acid residue in any one of positions 1 to 5 of SEQ ID NO: 1, 2, 3, 4 or 5 and ends with the amino acid residue in any one of positions 40 to 104 SEQ ID NO: 1, 2, 3, 4 or

5, does not reasonably provide enablement for 'isolated peptides consisting of 40 to 200 amino acid residues, wherein the peptide comprises an amino acid sequence which are at least 80 or 85% identical to SEQ ID NO: 1, 2, 3, 4 or 5' or for the subject matter in claim 51 which does not refer to a specific sequence. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims. .

The breadth of the instant claims contain amino acid sequences other than what is specified in the sequence disclosure. The specification states that substitutions, additions, or deletions may be made to the defined sequences; however, the specification provides no guidance as to what amino acids may be changed without causing a detrimental effect to the protein/peptide to be produced. It is unclear how the amino acid sequence can vary without upsetting the function of the polypeptide. It is unpredictable as to which amino acids could be removed and which could be added. While it is known that many amino acid substitutions are possible in any given protein/peptide, the position within the protein/peptide's sequence where amino acid substitutions can be made with a reasonable expectation of success are limited. Other positions are critical to the protein's structure/function relationship, e.g., such as various positions or regions directly involved in binding, catalysis in providing the correct three-dimensional spacial orientation of binding and catalytic sites. These regions can tolerate only very little or no substitutions. A 15-20% change in the coding region, as is encompassed by the present claims, could cause a detrimental effect to the protein/peptide to be produced and could

cause total negation of any epitopes which could induce an immune response or much less produce a functional protein or fragment. Additionally, selective point mutation to one key antigen residue could, in practical terms, eliminate the ability of an antibody to recognize this altered antigen. If the range of decreased binding ability after single point mutation of a protein antigen varies one could expect point mutations in the protein antigen to cause varying degrees of loss of protection, depending on the relative importance to the binding interaction of the altered residue. Alternatively, the combined effects of multiple changes in an antigenic determinant could again result in loss of protection. A protein having multiple antigenic sites, multiple point mutations, or accumulated point mutations at key residues could create a new antigen that is precipitously or progressively unrecognizable by any of the antibodies in the polyclonal pool. It is expensive and time consuming to make amino acid substitutions in a particular region of a protein in view of the possibilities for change in structure and the uncertainty as to what utility will be possessed. Further, the prior art has specifically taught that change to as little as one amino acid to the region of the IgA1 protease fragment currently claimed can completely abolish enzyme activity. See Lomholt, H. APMIS. Suppl. 62, vol 104. 1996, paragraph bridging page 15-16. A 20% change to a region ranging from 40 to 200 amino acids is quite large and it is unpredictable without specific guidance what deletions, insertions or substitutions could be made.

Applicants have provide no guidance to enable one of ordinary skill in the art how to determine, without undue experimentation, the effects of different amino acid substitutions and

the nature and extent of the changes that can be made. Given the lack of guidance contained in the specification and the unpredictability for determining acceptable amino acid substitutions, one of skill in the art could not make or use the broadly claimed invention without undue experimentation.

Response to Applicant's arguments:

Applicants argue that the claimed polypeptides when conjugated to a T-independent antigen are required to elicit a T-cell dependent immune response to that antigen. They argue that assays are provided by which a polypeptide can be tested to determine whether it elicits the proper immune response. These arguments have been fully and carefully considered but are not deemed persuasive. Variants are not enabled by the instant specification. The skilled artisan cannot envision the detailed structure of the encompassed polypeptides and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. A general method for screening numerous possibilities of peptide variants does not enable the instant claims. It would take undue experimentation to determine all variant sequences which can comprise 20% difference in amino acid sequence and then to individually conjugate and administer these peptides to determine if said changes still allow the peptide to function to elicit a T-cell dependent immune response to the antigen to which it is conjugated.

Enablement requires that the specification teach those in the art to make and use the invention without undue experimentation. Factors to be considered in determining whether a

disclosure would require undue experimentation include (1) the nature of the invention, (2) the state of the prior art, (3) the predictability or lack thereof in the art, (4) the amount of direction or guidance present, (5) the presence or absence of working examples, (6) the quantity of experimentation necessary, (7) the relative skill of those in the art, and (8) the breadth of the claims.

(1)The invention is drawn to N-terminal sequences ranging from 40-200 amino acids in length from a well known IgA1 protease which can differ from the known sequences by as much as 20%. (2, 3)The prior art has taught it is unpredictable to determine which amino acids could be removed and which could be added. While it is known that many amino acid substitutions are possible in any given protein/peptide, the position within the protein/peptide's sequence where amino acid substitutions can be made with a reasonable expectation of success are limited. Other positions are critical to the protein's structure/function relationship, e.g., such as various positions or regions directly involved in binding, catalysis in providing the correct three-dimensional spacial orientation of binding and catalytic sites. These regions can tolerate only very little or no substitutions. The combined effects of multiple changes in an antigenic determinant could again result in loss of function. Further, the prior art has specifically taught that change to as little as one amino acid to the region of the IgA1 protease fragment currently claimed can completely abolish enzyme activity. (4, 5) The specification provides no guidance as to what the changes could be and provides not working examples of fragments which differ

by 20% and are functional. (6-8) The relative skill in the art is high, but given the breadth of the claims the level of experimentation required to practice the invention would be undue.

With the exception of the proteins and protein fragments of SEQ ID NO:1, 2, 3, 4 and 5, the skilled artisan cannot envision the detailed structure of the encompassed polypeptides and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. It is noted that 20% is very large difference compared to the defined sequences and makes it even more unlikely that these sequences will maintain function. Applicants may wish to claim something with a closer degree of homology, such as 95%.

Claim Rejections - 35 USC § 112-Written Description

5. Claims 26-41 and 51 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The written description in this case only sets forth SEQ ID Nos: 1-5 and is not commensurate in scope with the claims drawn to homologous sequences or to *any* IgA protease from *N.gonorrhoeae, N.meningitidis* or *H.influenzae* as recited in claim 51.

Vas-Cath Inc. V. Mahurkar, 19 USPQ2d 1111, clearly states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the 'written description' inquiry,

whatever is now claimed." (See page 1117). The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See Vas-Cath at page 1116). Applicant is reminded that Vas-Cath makes clear that the written description provision of 35 USC 112 is severable from its enablement provision (see page 115).

Reiger et al (Glossary of Genetics and Cytogenetics, Classical and Molecular, 4th Ed., Springer-Verlay, Berlin, 1976) clearly define alleles as one of two or more alternative forms of a gene occupying the same locus on a particular chromosome..... and differing from other alleles of that locus at one or more mutational sites (page 17). Thus, the structure of naturally occurring allelic sequences are not defined. With the exception of SEQ ID NOs:1-5, the skilled artisan cannot envision the detailed structure of the encompassed polypeptides and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and a reference to a potential method of isolating it. See Fiers v. Revel, 25 USPQ 2d 1601 at 1606 (CAFC 1993) and Amgen Inc. V. Chugai Pharmaceutical Co. Lts., 18 USPQ2d 1016.

Furthermore, In The Reagents of the University of California v. Eli Lilly (43 USPQ2d 1398-1412), the court held that a generic statement which defines a genus of nucleic acids by only their functional activity does not provide an adequate written description of the genus. The court indicated that while Applicants are not required to disclose every species encompassed by a genus, the description of a genus is achieved by the recitation of a representative number of DNA

molecules, usually defined by a nucleotide sequence, falling within the scope of the claimed genus. At section B(1), the court states that "An adequate written description of a DNA...'requires a precise definition, such as by structure, formula, chemical name, or physical properties', not a mere wish or plan for obtaining the claimed chemical invention".

No disclosure, beyond the mere mention of homologous variants is made in the specification. This is insufficient to support the generic claims as provided by the Interim Written Description Guidelines published in the June 15, 1998 Federal Register at Volume 63, Number 114, pages 32639-32645.

Therefore, the full breadth of the claims meets the written description provisions of 35 USC 112, first paragraph.

Response to Applicant's arguments:

Applicants argue that claim 51 has been amended to include a recited function of the polypeptides and therefore adequate written description of the invention is provided. This has been fully and carefully considered but is not deemed persuasive. The instant claims encompass variant polypeptides which comprise amino acid sequences which have not yet been identified by Applicants. These sequences can contain up to a 20% difference which is very large. The skilled artisan cannot envision the detailed structure of the encompassed polypeptides and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and a reference to a potential method of isolating it.

Claim Rejections - 35 USC § 103

6. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

7. Claims 26-32 and 51 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lomholt et al (Mol. Microbiol., 1995, 15: 495-506) in view of Poulsen et al (Infect. Immun., 1989, 57(10): 3097-3105) and Lomholt, H. (APMIS Suppl.62, 104:5-28 1996) in further view of Killian et al (WO 90/11367).

Lomholt et al teach a polypeptide which is 100% identical to positions 1-104 of Applicants' SEQ ID NO:1 (100% identical to aa 1-40), 96.1% similar to Applicants' SEQ ID NO:2 (90.2% identical to aa 1-40), 95.4% similar to Applicants' SEQ ID NO:3 (90.2% identical to aa 1-40), 80.5% similar to Applicants' SEQ ID NO:4 (84.4% identical to aa 1-40) and 87.4% similar to Applicants' SEQ ID NO:5 (84.8% identical to aa 1-40). The sequence alignments were previously attached to the Office Action mailed 5/17/01. Lomholt teaches the complete sequence of the IgA gene from the HF13 strain of *N.meningitidis* as well as partial *IgA* sequences corresponding to the N-terminal half of the secreted IgA1 proteases of 18 *N.meningitidis* and 3 *H.influenzae* isolates. The N-terminal amino acid sequences corresponding to these nucleotide sequences are shown in Figure 3. Lomholt also teaches that the N-terminal region of the IgA1 protease is highly conserved is important for epitopes recognized by human

neutralizing antibodies induced during natural infection (see page 498, column 2). However, the N-terminal regions disclosed by Lomholt are all larger than 200 amino acids.

Poulsen et teach the cloning and sequencing of the IgA1 protease gene of *H.influenzae* serotype b. They also disclose a comparison of the deduced amino acid sequence of this IgA1 protease with that of a similar protease from *Neisseria gonorrhoeae* which revealed several domains with high degree of homology (see abstract). Poulsen et al also strikingly reveal that a stretch of 32 amino acids (aa 16 to 47) are identical in the two proteases except for a single conservative substitution thereby showing that the N-terminal part of the mature IgA1 protease has been evolutionary conserved, suggesting that it is essential to the translocation, enzymatic function or specificity of the protease molecule (see page 3104, column 1, second to last paragraph).

Lomholt teach vaccine aspects of bacterial immunoglobulin A1 proteases. The references teaches that the N-terminus is highly conserved among all serine type IgA1 proteases (page 14). It is further disclosed that a common surface exposed epitope residing in this region is displayed by large number of meningococcal IgA1 proteases and by at least one *H.influenzae* IgA1 protease (page 14). Lomholt teaches that the IgA1 enzyme or parts thereof may have a potential use in vaccines. Lomholt specifically teaches that IgA1 protease constitutes a putative carrier which at the same time may prevent coating of the bacteria by Fab fragments of IgA1.

Kilian et al recite IgA1 proteases and fragments of the IgA1 proteases. It is taught that these IgA1 proteases and fragments thereof may be used for the prevention of meningitis and also

for immunizing against allergic diseases, gonorrhoea and other diseases caused by IgA protease-producing bacteria (page 1). Killian also teach that the amino acid sequence of the one *H.influenzae* IgA1 protease and the *N.gonorrhoeae* protease are identical around the cleavage site of the leader peptide, thereby suggesting that the first 25 amino terminal amino acids constitute the signal peptide (page 17, lines 1-10). It is also stated that strikingly reveal that a stretch of 32 amino acids (aa 16 to 47) are identical in the two proteases except for a single conservative substitution thereby showing that the N-terminal part of the mature IgA1 protease has been evolutionary conserved, suggesting that it is essential to the enzymatic function or specificity of the protease molecule (page 17, lines 30-35). See claims 1 and 6 of Patent Serial No. WO/9011367 which recites IgA1 proteases and *fragments thereof.* The fragments thereof would include all fragments of the IgA1 proteases, including the ones instantly claimed.

It would have been prima facie obvious to obtain an N-terminal fragment from 1-200 amino acids from an IgA1 protease from *Neisseria or Haemophilus influenzae* known in the prior art such as those taught by Lomholt because the prior art, as evidenced by the teachings of Poulsen, Lomholt and Kilian, teach that the N-terminal region of the IgA1 protease is highly conserved among bacterial species and is essential to the enzymatic function and/or specificity of the protease molecule. It was well known in the art at the time the invention was made that peptides comprising conserved epitopes are extremely useful in bacterial detection methods and in immunization methods, particularly for raising antibodies against pathogens. Since Killian specifically teaches the use of fragments in IgA1 protease vaccines, it would have been obvious

to choose an N-terminal fragment of up to 200 amino acids from the proteases taught by Lomholt since one of ordinary skill in the art would naturally choose areas of the polypeptide which have proven to be highly conserved. The complete amino acid sequences of these IgA1 proteases and the specific location of their conserved regions were well known in the prior art at the time the invention was made and it would have been obvious to cleave off the highly conserved N-terminal region for use in a polypeptide detection system or as an immunogen or for other uses. Although the prior art does not teach the same intended use, "the ability to elicit a T-cell dependent immune response to a T-independent antigen when conjugated to said antigen" is an intended use only. A recitation of the intended use of the claimed invention must result in a structural difference between the claimed invention and the prior art in order to patentably distinguish the claimed invention from the prior art. If the prior art structure is capable of performing the intended use, then it meets the claim.

Response to Applicants' Arguments:

Applicants argue that the claimed polypeptides differ from the prior art peptides because they are able "to elicit a T-cell dependent immune response to a T-independent antigen when conjugated to said antigen". This has been fully and carefully considered but is not deemed persuasive. The peptides of the prior art have an identical structure to the peptides currently claimed so they would inherently possess the same functions, i.e., " the ability to elicit a T-cell dependent immune response to a T-independent antigen when conjugated to said antigen". The instant claims are not drawn to novel conjugate constructs, but solely to peptide fragments of

well known proteins. Further, the fragments of these proteins were already known in the prior art. The instant structures claimed do not differ from the structures taught in the prior art. Although the prior art does not teach the same intended use, "the ability to elicit a T-cell dependent immune response to a T-independent antigen when conjugated to said antigen" is an intended use only. A recitation of the intended use of the claimed invention must result in a structural difference between the claimed invention and the prior art in order to patentably distinguish the claimed invention from the prior art. If the prior art structure is capable of performing the intended use, then it meets the claim.

7. No claims are allowed.

8. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL.** See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

9. Correspondence regarding this application should be directed to Group Art Unit 1645. Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15,1989). The Group 1645 Fax number is (703) 308-4242 which is able to receive transmissions 24 hours/day, 7 days/week.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jennifer E. Graser whose telephone number is (703) 308-1742. The examiner can normally be reached on Monday-Friday from 7:00 AM-4:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Lynette Smith, can be reached on (703) 308-3909.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Jennifer Graser 11/5/03
Primary Examiner
Art Unit 1645